45. (New) The method of claim 25, wherein the amino acid sequence that encodes an epitope non-native to PE consists of between about 5 and about 15 amino acids.

REMARKS

With this amendment, claims 1-3, 7, 8, 12, 13, 24, 25, and 44-45 are pending in the present application and under examination. Claims 1, 2, 7, 12, 24, and 25 are amended. Claims 10, 27, 29, 30, 33, 37 and 38 are canceled without prejudice to subsequent revival. Claims 44 and 45 are added. Appendix A provides the version with markings to show change to the amended claims. Appendix B shows all pending claims currently under examination.

For convenience, the Examiner's rejections are addressed in the order in which they were presented in the December 20, 2001 Office Action.

Status of the claims

Claim 1 has been amended to more distinctly claim the *Pseudomonas* exotoxin A-like chimeric immunogens of the present invention. Instead of referring to "a non-native epitope domain comprising an amino acid sequence of between 5 and 1500 amino acids that encodes a non-native epitope", claim 1 now refers to "an epitope presenting domain located in between the translocation domain and ER retention domain comprising (i) an amino acid sequence of between 5 and 350 amino acids that encodes an epitope non-native to PE and (ii) two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein the epitope is inserted in between the two cysteine residues." This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page 27, line 28 to page 29, line 3.

Claim 2 has been amended to more distinctly claim the *Pseudomonas* exotoxin A-like chimeric immunogens of the present invention. Instead of referring to an immunogen "having the amino acid sequence of PE (SEQ ID NO:2) except that the

sequence of domain Ib comprises the non-native epitope between two cysteine residues of domain Ib and amino acid Glu at position 553 is deleted," claim 2 now refers to an immunogen "wherein the cell recognition domain is domain 1a of PE, the translocation domain is domain II of PE, and the ER retention domain is domain III of PE, wherein domain III lacks ADP ribosylation activity." This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page 22, line 18 to page 23, line 3.

Claim 7 has been amended to recite SEQ ID NO:2. This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the sequence listing.

Claim 12 has been amended to recite the phrase "wherein domain III lacks ADP ribosylation activity" in place of "except that amino acid Glu at position 553 of SEQ ID NO:2 is deleted". This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page 22, lines 26-31.

Claim 24 has been amended to more distinctly refer to the *Pseudomonas* exotoxin A-like chimeric immunogens of the present invention. Instead of referring to "a non-native epitope domain comprising an amino acid sequence of between 5 and 1500 amino acids that encodes a non-native epitope," claim 24 now refers to "an epitope presenting domain located in between the translocation domain and ER retention domain comprising (i) an amino acid sequence of between 5 and 350 amino acids that encodes an epitope non-native to PE and (ii) two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein the epitope is inserted in between the two cysteine residues." This amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page 27, line 28 to page 29, line 3.

Claim 25 has been amended to recite the phrase "between about 5 and about 50 amino acids" in place of the phrase "no more than about 30 amino acids". This

amendment adds no new matter. Support for this amendment can be found, e.g., in the claims as filed and in the specification on page 28, lines 4-6.

Claims 44 and 45 have been added. These claims add no new matter. Support for new claims 44 and 45 can be found, e.g., in the claims as filed and in the specification on page 28, lines 4-6.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

The Examiner has rejected claims 27, 29, 33, and 37-38 under 35 U.S.C. § 112, first paragraph. According to the Examiner, the specification does not reasonably provide enablement for the use of the immunogen for the stimulation of a protective immune response for the prophylactic or therapeutic treatment of any disease. The Examiner believes that the present claims are not enabled because the "ability to predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic". Applicants respectfully traverse.

The present application provides methods of making the claimed chimeric immunogens and methods of administering them to a subject. Furthermore, as demonstrated in the specification, sera from rabbits injected with chimeric proteins containing either an MN or Thai-E subtype strain of HIV-1 were able to neutralize infectivity of HIV-1 (see examples section, page 49-52). Applicants submit that the ability to neutralize HIV-1 antigens is indicative of the ability of the chimeric immunogen to stimulate a protective immune response.

Accordingly, Applicants do not agree or concede that the specification is not enabling for the use of an immunogen for the stimulation of a protective immune response for the treatment of disease. To expedite prosecution, however, Applicants have canceled claims 27, 29-30, 33 and 37-38. The amendment is believed to obviate the Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph, indefiniteness

"Substantially identical to a sequence of PE domain II"

Claim 1 has been rejected as allegedly indefinite for reciting the phrase "substantially identical to a sequence of PE domain II". Applicants respectfully traverse. On page 16, lines 6-13 of the specification, Applicants define the phrase substantially identical to a sequence of PE domain II to refer to a sequence that has at least 60%, 80%, 90%, 95%, or 98% nucleotide or amino acid sequence identity to the sequence of PE domain II. Accordingly, one of skill in the art would understand that a sequence that is substantially identical to a sequence of PE domain II is a sequence that has 60%-100% sequence identity to the sequence of PE domain II. Furthermore, on page 16, line 15 to page 18, line 24, Applicants provide examples of how one skilled in the art would determine percent identity and provide statistical parameters defining percent identity.

"Sufficient to effect translocation to a cell cytosol"

Claim 1 has been rejected as allegedly indefinite for reciting the phrase "sufficient to effect translocation to a cell cytosol". Applicants respectfully traverse. On page 26, line 30 to page 27, line 25 of the specification, a translocation domain comprising an amino acid sequence sufficient to effect translocation to a cell cytosol is defined as a domain that functions to translocate chimeric proteins that have been endocytosed by the cell into the cytosol. Applicants explain that the amino acid sequence sufficient to effect translocation can derive from the translocation domain of native PE which spans amino acids 253-364. Furthermore, in the specification on page 32, line 20 to page 33, line 5, Applicants provide methods of testing whether a putative amino acid sequence functions as a translocation domain. Accordingly, one of skill would understand the meaning of the phrase "sufficient to effect translocation to a cell cytosol." Applicants therefore respectfully request that the rejection be withdrawn.

"Encodes a non-native epitope"

Claim 1 has been rejected as allegedly indefinite for reciting the phrase "encodes a non-native epitope". In order to address the Examiner's concerns, the phrase has been amended to recite "encodes an epitope non-native to PE". The amendment is believed to obviate the Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

"A non-toxic *Pseudomonas* exotoxin A-like chimeric immunogen"

Claim 1 has been rejected as allegedly indefinite for reciting the phrase "A non-toxic *Pseudomonas* exotoxin-A like chimeric immunogen". Applicants respectfully traverse. Applicants define the non-toxic *Pseudomonas* exotoxin-A like chimeric immunogen both structurally and functionally. On page 23, line 7 to page 24, line 5 of the specification, Applicants teach that *Pseudomonas* exotoxin-A-like chimeric immunogens are polypeptides having structural domains organized in the same sequence as the four structural domains of PE wherein the structural domains, although not identical in sequence, are capable of performing the same functions as the four structural domains of PE, e.g., domain 1a has cell recognition capabilities, domain II has cytosolic translocation capabilities, domain Ib has no known function but is useful for antigen presentation, and domain III has endoplasmic reticulum retention capabilities. On pages 24-31 of the specification, Applicants further define the *Pseudomonas* exotoxin-A-like chimeric immunogen domains in detail. The skilled practitioner, after reading the specification, would be able to recognize the *Pseudomonas* exotoxin-A-like chimeric immunogens of the present invention.

The Examiner objects to the term non-toxic. In the specification on page 22, lines 18-31, Applicants teach that PE is non-toxic if it lacks EF2 ADP ribosylation activity. Specifically deleting amino acid E553 from domain III of PE detoxifies the molecule. The skilled practitioner would understand, therefore, that a non-toxic PE-like chimeric immunogen is a PE-like chimeric immunogen that lacks EF2 ADP ribosylation activity.

"an amino acid sequence of between 5 and 1500 amino acids"

Claims 1, 24, 27 and 33 have been rejected as allegedly indefinite for reciting epitopes of up to 1500 amino acids. In order to address the Examiner's concerns, the phrase has been amended to recite epitopes of between about 5 and about 350 amino acids. The amendment is believed to obviate the Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

"having the amino acid sequence of PE ΔE553"

Claim 2 has been rejected as allegedly indefinite for reciting the phrase "having the amino acid sequence of PE ΔE553". To expedite prosecution, claim 2 has been amended to delete the phrase "having the amino acid sequence of PE ΔE553". Applicants' therefore respectfully request that the rejection be withdrawn.

Reference Sequence ID

Claim 7 has been rejected as allegedly vague and indefinite for not referring to a reference sequence in the claim. To expedite prosecution, claim 7 has been amended to refer to a SEQ ID NO. Applicants' therefore respectfully request that the rejection be withdrawn.

Claim 8

Claim 8 has been rejected as allegedly unclear because, according to the Examiner, claim 8 sets forth that the translocation domain is domain II of PE and depends from claim 1, yet claim 1 defines domain II to differ from the sequence of PE domain II. Applicants respectfully traverse. Claim 1 defines the translocation domain as comprising an amino acid sequence "substantially identical" to a sequence of PE domain II. Page 16, lines 5-14 of the specification defines "substantially identical" to refer to two sequence that have *at least* 60%, 80%, 90%, 95% or 98% identity. Accordingly, the translocation

domain defined in claim 1 may have 100% identity to PE domain II. Applicants therefore respectfully request that the rejection be withdrawn.

"the non -native epitope domain comprise a cysteine-cysteine loop that comprises the non-native epitope"

Claim 9 has been rejected as allegedly indefinite for reciting the phrase "the non -native epitope domain comprise a cysteine-cysteine loop that comprises the non-native epitope". To expedite prosecution, claim 9 has been canceled. Applicants' therefore respectfully request that the rejection be withdrawn.

"A non-native epitope inserted between two cysteine residues of domain Ib of PE"

Claim 10 has been rejected as allegedly indefinite for reciting the phrase "a non-native epitope inserted between two cysteine residues of domain Ib of PE". To expedite prosecution, claim 10 has been canceled. Applicants' therefore respectfully request that the rejection be withdrawn.

"Domain III of PE comprising the mutation ΔE553"

Claim 12 has been rejected as allegedly indefinite for reciting the phrase "Domain III of PE comprising the mutation ΔE553". In order to address the Examiner's concerns, the phrase has been amended to recite "wherein domain III lacks ADP ribosylation activity". The amendment is believed to obviate the Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

Claim 24

Claim 24 had been rejected as being incomplete for allegedly omitting essential steps. In order to address the Examiner's concerns, the step of "collecting antiserum" has been added to the claim. The amendment is believed to obviate the

Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

"No more than about 30 amino acids"

Claim 25 has been rejected as broadening the scope of the claim from which it depends. In response, Applicant's have amended the claim to recite a lower limit of about 5 amino acids. Applicant's have also amended the claim to recite an upper limit of about 50 amino acids. The amendment is believed to obviate the Examiner's concerns. Applicants' therefore respectfully request that the rejection be withdrawn.

Claims 27, 30, 37, and 38

Claims 27, 30, and 37-38 have been rejected as allegedly indefinite. Applicant's have responded to these rejections in the previous section entitled "Rejection under 35 U.S.C. § 112, first paragraph, enablement." Accordingly, Applicants respectfully request that the rejection be withdrawn.

Claim 33

Claim 33 is rejected as allegedly indefinite for not defining the subject as one that is immunocompetent. To expedite prosecution, the claim has been withdrawn. Applicants' therefore respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Pending claims 1, 7, 8, 12, and 33 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,328,984 ("'984"). The rejection states that because the '984 patent teaches domain Ib as a site for efficient insertion of specific peptides, the claims are anticipated.

To the extent the rejection applies to the claims as amended, Applicants respectfully traverse. The '984 patent does not expressly or inherently set forth the

element that the amino acid sequence encoding the desired peptide is inserted in between two cysteine residues native to the Ib domain of PE.

For a rejection of claims under § 102 to be properly founded, the Examiner must establish that a single prior art reference either expressly or inherently discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Verdegaal Bros. V. Union Oil Co. Of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991), the Federal Circuit held that:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Id.* at 1010.

Anticipation can be found, therefore, only when a cited reference discloses all of the elements, features or limitations of the presently claimed invention.

The rejection cites the '984 patent as the basis for the 102(b) rejection. Applicants respectfully submit that the '984 patent does not disclose every element of the presently claimed invention and, thus, cannot form the basis for a 102(b) rejection. Namely, the '984 patent neither expressly nor inherently discloses that the *Pseudomonas* exotoxin A-like chimeric immunogens of the invention contain two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein the amino acid encoding the desired epitope is inserted in between the two cysteine residues.

The '984 patent fails to disclose an epitope presenting domain comprising two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein an amino acid sequence encoding an epitope is inserted between the two cysteine residues

The '984 patent fails to disclose an epitope presenting domain comprising two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein an amino acid sequence encoding an epitope is inserted between the two cysteine residues. In the '984 patent, the inventors contemplate introducing specific peptides, e.g., somatostatin, into a chimeric *Pseudomonas* exotoxin by deleting the entire Ib domain that is native to the *Pseudomonas* exotoxin and inserting a desired peptide in its place.

In contrast to the chimeric *Pseudomonas* exotoxins claimed in the '984 patent, the chimeric *Pseudomonas* exotoxins claimed in the present application retain the cysteine-cysteine disulfide bonded loop native to the 1b domain of PE. In the '984 patent, the two cysteine residues native to the 1b domain of PE are deleted along with the rest of the 1b domain. In the present application, the two cysteine residues native to PE are retained. The two retained cysteine residues form the cysteine-cysteine disulfide bonded loop native to PE and an amino acid sequence encoding a desired epitope is inserted in the loop.

In nature, many epitopes are presented to the immune system within a cysteine-cysteine disulfide-bonded loop. The chimeric immunogens of the present invention advantageously present these epitopes to the immune system in their native conformation.

As taught in the specification, the PE immunotoxin comprises four domains. Domain 1a of PE extends from amino acids 1-252. Domain II extends from amino acids 253-364. Domain Ib spans from amino acids 365-399. Domain III spans amino acids 400-613.

Applicants claim a *Pseudomonas* exotoxin A-like chimeric immunogen wherein the cysteine residues and disulfide bond native to the Ib domain of PE are conserved. As previously mentioned, domain Ib of the native *Pseudomonas* exotoxin

spans amino acids 365 to 399. Domain Ib is structurally characterized by a disulfide bond between two cysteines at positions 372 and 379. Domain Ib has been demonstrated to be not essential for cell binding, translocation, ER retention or ADP ribosylation activity.

The '984 patent, in column 12, discloses chimeric toxins containing somatostatin-14 with or without cysteines inserted in place of the Ib domain of PE. The rejection mischaracterizes this disclosure. In column 12 of the '984 patent, the inventors are not referring to the insertion of somatostatin between the two cysteines that form a disulfide bonded loop native to the Ib domain of PE but are instead referring to the insertion of somatostatin in the location of the deleted Ib domain. The phrase "with or without cysteines" is referring to the cysteines that comprise the somatostatin sequence and not the cysteines native to the Ib domain of PE. (See figure 8 and column 3, lines 7-10 of the '984 patent). As explained later in the paragraph, the inventors were trying to determine if the Ib domain of the *Pseudomonas* exotoxin could be replaced with foreign amino acid sequences while keeping intact its membrane translocation and cytotoxic activities. The inventors found that replacing the Ib region with either SEQ ID NO:2 (somatostatin with somatostatin cysteine residues) or SEQ ID NO:3 (somatostatin without its native cysteine residues) did not interfere with PE membrane translocation or cytotoxic activity.

In the '984 patent, the entire Ib domain of the *Pseudomonas* exotoxin was re-engineered to create the chimeric proteins containing somatostatin. Accordingly, the '984 patent contemplates a *Pseudomonas* exotoxin wherein the Ib domain is deleted and an amino acid sequence encoding a desired peptide is inserted in its place. In the present application, the PE-like immunogen retains the cysteine residues native to the Ib domain of PE. By retaining the native cysteines, the cysteine-cysteine disulfide bonded loop structure native to PE is also retained. Epitopes can thereby be presented by the chimeric immunogen in near-native conformation and are better able to provoke an immune response against the antigen (see specification on page 3, lines 30 to page 4 , line 2).

Thus, the '984 patent neither inherently nor explicitly discloses the features of the present invention. The '984 patent does not disclose that the desired amino acid sequence can be inserted in between the native PE cysteine residues thereby preserving the cysteine-cysteine disulfide bonded loop native to the PE immunogen. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103

Pending claim 2 is rejected under 35 U.S.C. § 103 as being obvious over the '984 patent, pending claims 24, 25 and 33 are rejected as being obvious over the '984 in view of U.S. Patent No. 6,074,644 ("'644") and pending claims 1-3, 7-8, 12-13, 24-25, and 33 are rejected as being obvious over Cryz *et al.* in view of Moore and the '984 patent.

Applicants respectfully traverse. As set forth in the M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." As the Federal Circuit has also stated, "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel,* 35 U.S.P.Q.2d 1210, 1216 (Fed. Cir. 1995).

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

There is no Suggestion or Motivation to Modify the References

Applicants assert that there is simply no motivation or suggestion provided in the cited references to modify the 1b region of a *Pseudomonas* exotoxin as claimed by the present invention, e.g., to insert an epitope in between the cysteine residues native to the 1b domain of PE. As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Before the advent of the present invention, there was no motivation to substitute somatostatin or any other peptide between the two cysteine residues native to the 1b domain of PE. In both the '984 and '644 patents, the 1b domain native to PE was described as nonessential. Residues comprising the 1b domain including the cysteines native to the 1b domain were deleted. Accordingly, there was no motivation to use the 1b domain residues for any purpose including antigen presenting purposes. The discovery that an amino acid sequence encoding a non-native epitope to PE could be inserted into the cysteine-cysteine disulfide bonded loop of the 1b domain and be advantageously presented to the immune system in the loop structure was unexpected.

In the present Office Action, the Examiner refers Applicants to U.S. patent '984, U.S. patent '644, Cryz *et al.*, and Moore in an attempt to demonstrate that the invention claimed in the present application is obvious. These references, however, neither teach nor suggest that cysteine-cysteine disulfide bonded loops of carrier proteins can be used to present immunogenic peptides in near native conformations to the immune system.

As previously discussed, the '984 patent teaches insertion of a peptide in place of the deleted 1b domain of PE for delivery of the peptide across cellular membranes into the cytosol of target cells. There is neither a teaching nor suggestion to

use the cysteine residues of the 1b domain to present the peptides in a disulfide bonded loop formation.

The '644 patent describes a *Pseudomonas* exotoxin lacking domain 1, wherein half or more of domain 1b is replaced with an antibody fragment. Not only is there neither a teaching nor suggestion to insert an antigenic peptide between the cysteine residues native to the 1b domain of PE, this reference actually *teaches away* from such an insertion. In lines 8-16 of column 9, the '644 patent teaches that in order to insert the antibody fragment in domain 1b, the cysteine in the 1b region should be mutated to serine in order to prevent disulfide linkage formation.

The Cryz reference describes a peptide-toxin conjugate There is neither a teaching nor suggestion that an insertion of an epitope within a cysteine-cysteine disulfide bonded loop formed by the toxin would be desirable.

Finally, the Moore reference cited by the Examiner neither teaches nor suggests that a peptide can be inserted within a cysteine-cysteine loop of a carrier protein and still retain its immunogenicity. The Moore references in fact suggests just the opposite. As explained by the Examiner, the Moore reference teaches the importance of retaining cysteine loop structures of synthetic peptides for the purpose of stabilizing peptide immunogens to induce the desired immune response. In direct contrast, the present application teaches that the cysteine loop structure need not be retained in the peptide because instead, the peptide can be inserted into a cysteine loop of a carrier protein and thereby retain its immunogenicity.

In summary, before the advent of the present invention, the skilled practitioner would not be motivated to insert either an epitope or any other antigenic peptide in between the cysteine residues native to the 1b region of the *Pseudomonas* exotoxin. Accordingly, Applicants respectfully request that the rejection be withdrawn.

There is no Reasonable Expectation of Success

In addition to a lack of motivation to insert an epitope in between the cysteine residues native to the 1b region of the *Pseudomonas* exotoxin, there is also no

reasonable expectation of success that insertion of an epitope in that region would be an effective way to present an epitope to the immune system.

Moore teaches the importance of retaining cysteine loop structures of the synthetic peptides. Cryz teaches that an immunogenic peptide for vaccine formulation is highly immunogenic if it retains its own cysteine loop formation. The '644 patent teaches that the cysteine in domain 1b of PE should be deleted so as not to interfere with antibody presentation to the immune system. Applicants could not have expected, therefore, that an epitope that does not retain its own native structure but instead is inserted in between cysteine resides of the 1b domain of PE will retain its immunogenicity and be properly presented to the immune system.

The Cited Art References Do Not Teach All Limitations of the Claims

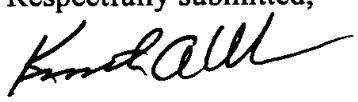
The prior art references must teach or suggest all of the limitations of the claims. *In re Wilson,* 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicant's claim a *Pseudomonas* exotoxin comprising an epitope inserted in between two cysteine residues native to the 1b domain of PE. As previously discussed, the cited references neither teach nor suggest such a composition. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (once amended) A non-toxic *Pseudomonas* exotoxin A-like ("PE-like") chimeric immunogen comprising: (1) a cell recognition domain of between 10 and 1500 amino acids that binds to a cell surface receptor; (2) a translocation domain comprising an amino acid sequence substantially identical to a sequence of PE domain II sufficient to effect translocation to a cell cytosol; [(3) a non-native epitope domain comprising an amino acid sequence of between 5 and 1500 amino acids that encodes a non-native epitope; and (4) an amino acid sequence encoding an endoplasmic reticulum ("ER") retention domain that comprises an ER retention sequence] (3) an amino acid sequence encoding an endoplasmic reticulum ("ER") retention domain that comprises an ER retention sequence, (4) an epitope presenting domain located in between the translocation domain and ER retention domain comprising (i) an amino acid sequence of between 5 and 350 amino acids that encodes an epitope non-native to PE and (ii) two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein the epitope is inserted in between the two cysteine residues.

2. (once amended) The immunogen of claim 1, [having the amino acid sequence of PE (SEQ ID NO:2) except that the sequence of domain Ib comprises the non-native epitope between two cysteine residues of domain Ib and amino acid Glu at position 553 is deleted] wherein the cell recognition domain is domain 1a of PE, the translocation domain is domain II of PE, and the ER retention domain is domain III of PE, wherein domain III lacks ADP ribosylation activity.

7. (once amended) The immunogen of claim 1 wherein the translocation domain comprises amino acids 280 to 364 of [domain II of PE] SEQ ID NO:2.

12. (once amended) The immunogen of claim 1 wherein the ER retention domain is domain III of PE [except that amino acid Glu at position 553 of SEQ ID NO:2 is deleted], wherein domain III lacks ADP ribosylation activity.

24. (once amended) A method of producing antibodies against an [non-native] epitope non-native to PE, wherein the [non-native] epitope [naturally] exists within a cysteine-cysteine loop comprising the steps of:

(i) inoculating an animal with a non-toxic *Pseudomonas* exotoxin A-like ("PE-like") chimeric immunogen, the PE-like chimeric immunogen comprising: [(1) a cell recognition domain of between 10 and 1500 amino acids that binds to a cell surface receptor; (2) a translocation domain comprising an amino acid sequence substantially identical to a sequence of PE domain II sufficient to effect translocation to a cell cytosol; (3) a non-native epitope domain comprising a cysteine-cysteine loop that contains within the loop an amino acid sequence of between 5 and 1500 amino acids that encodes a non-native epitope; and (4) an amino acid sequence encoding an endoplasmic reticulum ("ER") retention domain that comprises an ER retention sequence] (1) a cell recognition domain of between 10 and 1500 amino acids that binds to a cell surface receptor; (2) a translocation domain comprising an amino acid sequence substantially identical to a sequence of PE domain II sufficient to effect translocation to a cell cytosol; (3) an amino acid sequence encoding an endoplasmic reticulum ("ER") retention domain that comprises an ER retention sequence, (4) an epitope presenting domain located in between the translocation domain and ER retention domain comprising (i) an amino acid sequence of between 5 and 350 amino acids that encodes an epitope non-native to PE and (ii) two cysteine residues native to PE that form a cysteine-cysteine disulfide bonded loop, wherein the epitope is inserted in between the two cysteine residues.

(ii) collecting antiserum

25. (once amended) The method of claim 24 wherein the [cysteine-cysteine loop comprises no more than about 30 amino acids] amino acid sequence that encodes an epitope non-native to PE consists of between about 5 and about 50 amino acids.